

## First-line Treatment of Oral Candidiasis in Adults

Developed in collaboration with an advisory committee consisting of Québec clinicians and experts.

Validated by the Comité d'excellence clinique en usage optimal du médicament, des protocoles médicaux nationaux et ordonnances of the Institut national d'excellence en santé et en services sociaux (INESSS).

### CLINICAL SITUATION OR TARGET POPULATION

Person aged 18 years and older with one or several of the following clinical signs and symptoms:

- ▶ Sensation of burning, discomfort or general pain in the mouth or at the corners of the mouth, which worsens when eating food<sup>1</sup>
- ▶ White patches that can be scraped away more or less easily; redness on the mucous membranes of the mouth.
- ▶ Cracked skin or slight bleeding at the corners of the mouth, which may extend to marionette lines.
- ▶ Total or partial loss of papillae on the surface of the tongue.

### CONTRAINDICATIONS TO THE APPLICATION OF THIS PROTOCOL

- ▶ Contraindication or history of allergic reaction to the recommended medication.
- ▶ Known case of refractory oral candidiasis.
- ▶ Oral candidiasis recurrence within one month of initial treatment.
- ▶ White patches that appear unilaterally on the tongue or cannot be scraped away.
- ▶ Bite or sore marks on the inside of the cheeks or on the tongue.
- ▶ Gum or submaxillary swelling.
- ▶ Surgery, injury, trauma, cut, burns in the mouth, or oral health problems (e.g. viral, bacterial or fungal infections) within the past two (2) weeks.
- ▶ Oral pain, localized or unilateral.
- ▶ Difficulty in swallowing, pain or burning sensation in the sternum or chest (suggesting esophageal candidiasis).
- ▶ Constant burning sensation that lessens when eating food (suggesting stomatopyrosis).

### INSTRUCTIONS

#### 1. ASSESSMENT OF HEALTH STATUS

##### 1.1 Symptoms

**Check for presence of the following symptoms (suggesting oral candidiasis)<sup>2</sup>:**

- ▶ Sensation of burning, discomfort or general pain in the mouth or at the corners of the mouth, which worsens when eating food<sup>1</sup>
- ▶ Woolly feeling or metallic taste in the mouth

**Check for presence of the following alarm symptoms:**

- ▶ Difficulty in swallowing, pain or burning sensation in the sternum or chest (suggesting ryingeal).
- ▶ Constant burning sensation that lessens when eating food (suggesting stomatopyrosis).
- ▶ Oral pain, localized or unilateral.

<sup>1</sup>. May present as a refusal to eat in individuals with reduced autonomy, difficulties communicating or major neurocognitive disorders.

<sup>2</sup>. Oral candidiasis can be asymptomatic despite apparent clinical signs. Absence of symptoms should not stop medical team from initiating first-line treatment.

## 1.2 Health history

### Check for presence of factors that may cause oral candidiasis:

- ▶ History of mouth dryness
- ▶ Diabetes
- ▶ HIV/AIDS
- ▶ Dental prosthesis

\*See Appendix I for a comprehensive list of risk factors associated with oral candidiasis.

### Inquire about:

- ▶ History of oral or esophageal candidiasis (number of episodes, approximate dates)
  - Known case of refractory candidiasis;
  - Oral candidiasis recurrence within one month of initial treatment.
- ▶ Surgery, injury, trauma, cut, recent burn in the mouth, or oral health problems (e.g. viral, bacterial or fungal infections) within the past two (2) weeks.

## 1.3 Medication history

### Ask about usage of:

- ▶ Any antifungal drug for the treatment of oral candidiasis in the past month.
- ▶ Inhaled corticosteroids for the treatment of various respiratory illnesses.

### Inquire about:

- ▶ Patient's history of allergic reaction to any antifungal drug administered in first-line treatment of oral candidiasis (nystatin, miconazole, clotrimazole, fluconazole).

## 1.4 Physical examination

### Check for presence of one or several of the following signs in the person's mouth (suggesting oral candidiasis):

- ▶ White patches having the appearance of milk curds on the mucous membranes of the mouth, which are more or less easy to scrape away with a tongue blade or other instruments (erythema may be visible under patches, and minor bleeding may occur).
- ▶ Partial or total loss of papillae on the surface of the tongue.
- ▶ Erythema or cracked skin at the corners of the mouth (suggesting perleche), which may extend to marionette lines.
- ▶ If the person wears dental prostheses<sup>3</sup>, erythema on areas in contact with them (i.e., palate or gums).

\*See Appendix II for pictures of various forms of oral candidiasis.

### Check for the following alarm signs:

- ▶ Fever<sup>4</sup>
- ▶ Ulcers
- ▶ Unilateral white patches on the tongue
- ▶ White patches that cannot be scraped away
- ▶ Bite or sore marks on the inside of the cheeks or on the tongue.
- ▶ Gum swelling
- ▶ Submaxillary swelling

\*See Appendix III for images of other mouth diseases not to be mistaken with oral candidiasis.

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<sup>3</sup>. Individuals not wearing dental prostheses may also be affected by erythematous candidiasis.

<sup>4</sup>. Oral candidiasis does not normally cause fever in affected individuals.

## 2. LABORATORY TESTS

- ▶ Not required <sup>5</sup>

## 3. TREATMENT APPROACH

### 3.1 Therapeutic objective

Eliminating suggestive symptoms and signs of oral candidiasis and identified before the start of treatment.

### 3.2 General information on pharmacological treatments

The following general information on pharmacological treatments of oral candidiasis is not exhaustive.

GENERAL INFORMATION ON PHARMACOLOGICAL TREATMENTS		
	Nystatin	Fluconazole
<b>Forms available and reimbursement particulars</b>	<u>Oral suspension</u> (100 000 U/ml)	<u>Capsule</u> (150 mg) and <u>tablet</u> (50 and 100 mg) <u>Oral suspension</u> (10 mg/mL) (RAMQ-Exception drug, code A19) <sup>6</sup>
<b>Contraindications</b>	History of allergic reaction to nystatin or other ingredients in the formulation	History of allergic reaction to fluconazole, excipients of drug product or compounds similar to azoles Do not administer with other drugs that may prolong the QT interval AND metabolized through CYP3A4.
<b>Precautions</b>	Cannot be used to treat systemic candidiasis Diabetes and tooth decay (oral suspension): contains 50 % sucrose (i.e., 2.5 g/5 mL dose)	Liver dysfunction: Interrupt administration of fluconazole at the first sign or symptom of liver dysfunction due to fluconazole Kidney failure: dosage adjustment required <sup>7</sup> Pregnancy and breast-feeding
<b>Most common drug adverse effects</b>	<ul style="list-style-type: none"><li>▶ Gastrointestinal disorders: diarrhea, nausea, vomiting</li><li>▶ Local sensibility or irritation</li></ul>	<ul style="list-style-type: none"><li>▶ Gastrointestinal disorders: diarrhea, nausea, vomiting, abdominal pains</li><li>▶ Headaches</li></ul>
<b>Most significant drug interactions</b>	None	↑ concentration of metabolized drugs by cytochromes P450 3A4, 2C9 and 2C19, including: <ul style="list-style-type: none"><li>• Calcium channel blockers</li><li>• Carbamazepine, phenytoin</li><li>• Cyclosporine, sirolimus, tacrolimus</li><li>• Fentanyl</li><li>• Benzodiazepines</li><li>• Statins</li><li>• Tamoxifen</li></ul> Warfarine: ↑ risks of bleeding Rifampine (CYP3A4 inducing agent): ↓ concentration of fluconazole Exercise caution if fluconazole must be administered with other prescribed drugs that may prolong the QT interval.

<sup>5</sup> Oral candidiasis is normally easy to detect during physical and visual examination of the mouth. Lab tests may have to be conducted in the case of recurrences, complications, treatment failure or any doubt as to the presence of oral candidiasis.

<sup>6</sup> The indication recognized for payment under the RAMQ public prescription drug insurance plan is:

- Treatment of oropharyngeal candidiasis in patients for whom conventional therapy proves ineffective or is poorly tolerated and who cannot receive fluconazole tablets.

<sup>7</sup> See section 3.3 for posology adjustment procedures.

### 3.3 Choosing the pharmacological treatment

TREATMENT OF ORAL CANDIDIASIS IN ADULTS WHO WEAR OR DO NOT WEAR DENTAL PROSTHESES			
Antifungal	Posology		Treatment duration
<b>Fist-line Treatment</b>			
<b>Nystatin</b> (oral suspension)	Rinse mouth with 5 mL (500 000 U) QID for minimum 2 minutes <sup>1</sup> , then spit out or swallow		14 days
<b>If nystatin cannot be administered<sup>2</sup></b>			
<b>Fluconazole</b> (tablet or capsule) <i>Authorized prescribers only</i>	Clcr (ml/min)	> 50	200 mg PO DIE
		21 to 50	100 mg PO DIE
		11 to 20	50 mg PO DIE
		Hemodialyzed	200 mg PO after each dialysis session
			7 to 14 days

1. If not possible for the person to comply with contact time or difficult to open and rinse the mouth, the medication can be applied with a clean soft bristled toothbrush. In these circumstances, popsicles made with nystatin could be a replacement option.
2. For instance, a person with major cognitive disorder or unable to open the mouth.

### 4. INFORMATION TO BE PROVIDED

Discuss the following with the person, his or her caregiver or the care team:

POPULATIONS/CONDITIONS	INFORMATION TO BE PROVIDED
<b>All</b>	<ul style="list-style-type: none"> <li>• At each treatment, comply with the recommended minimum contact time (2 minutes) to ensure the effectiveness of nystatin.</li> <li>• Nystatin may be spit out or safely swallowed after each treatment.</li> <li>• Avoid drinking or eating for 30 minutes after each treatment.</li> <li>• Maintain good oral hygiene.</li> </ul>
<b>Diabetes or HIV/AIDS</b>	<ul style="list-style-type: none"> <li>• Properly follow or continue anti-diabetes or antiretroviral therapy.</li> <li>• As a precaution, it would be preferable for individuals with diabetes to spit out nystatin after each treatment, because of nystatin's high sucrose content (50% - 2.5 g/5 ml dose)</li> </ul>
<b>Dental prostheses</b>	<ul style="list-style-type: none"> <li>• Clean and disinfect dental prostheses before each treatment.</li> <li>• Remove prostheses before rinsing mouth with nystatin.</li> <li>• In the event of redness or erythema on areas in contact with the prostheses (palate or gums), apply QID a thin layer of nystatin (cream/ointment, 100 000 U/g or oral suspension), clotrimazole (cream, 1%) or miconazole nitrate (cream, 2%) on the surface of the prostheses that is in contact with gums throughout the antifungal treatment. Dental prostheses can also be brushed with nystatin oral suspension (100 000 U/ml).</li> <li>• Remove dental prostheses and let soak overnight (lukewarm water)</li> <li>• Clean and disinfect the denture cleaning case prior to each use.</li> </ul>
<b>Use of inhalers containing corticosteroids</b>	<ul style="list-style-type: none"> <li>• Rinse mouth and gargle with water after each inhalation.</li> </ul>
<b>Cracked skin or slight bleeding at the corners of the mouth or marionette lines</b>	<ul style="list-style-type: none"> <li>• Apply QID for 14 days a thin layer of nystatin (cream/ointment, 100 000 U/g), clotrimazole (cream, 1%) or miconazole nitrate (cream, 2%) on erythema or cracked skin at the corners of the mouth.</li> <li>• Avoid licking cracked, sore skin or using a lip balm throughout the treatment.</li> </ul>
<b>Xerostomia</b>	<ul style="list-style-type: none"> <li>• Encourage saliva production (e.g. sugar-free xylitol-sweetened gum).</li> <li>• Drink water regularly.</li> <li>• Use artificial saliva, as required.</li> </ul>

Together with the interprofessional team, optimally manage the modifiable risk factors fostering development of oral candidiasis, if necessary.

## 5. FOLLOW-UP FOR INDIVIDUALS IN RESIDENTIAL FACILITIES

- ▶ Detect adverse effects.
- ▶ Document suggestive symptoms and signs of oral candidiasis **7 days** after start of treatment and **at the end of treatment**, i.e., when the last dose of antifungal medication is administered.

## 6. SITUATIONS REQUIRING FURTHER INVESTIGATION OR REASSESSMENT

- ▶ Difficulty in swallowing, pain or burning sensation in the sternum or chest during treatment (suggesting esophageal candidiasis)
- ▶ Presence or outbreak of fever during treatment.
- ▶ Aggravation of the symptoms and signs seven days after the start of the treatment.
- ▶ Persistence of the symptoms and signs at the end of the treatment.
- ▶ Allergic reaction or intolerance to prescribed antifungal.

## REFERENCES

This protocol is based on the latest scientific data and best practice recommendations, which were enhanced with contextual information and experiential knowledge provided by Québec clinicians, experts and patients. For further details on the process used to develop this medical protocol and to consult the references, see the [report in support of this protocol](#).

## APPENDIX I

RISK FACTORS ASSOCIATED WITH ORAL CANDIDIASIS	MODIFIABLE	POTENTIALLY MODIFIABLE	NON-MODIFIABLE
▶ <b>Old age with precarious medical condition</b>			✓
▶ <b>Recent use of systemic antibiotics</b>			✓
▶ <b>Mouth dryness</b>			
○ Dehydration	✓		
○ History of radiotherapy - head and neck			✓
○ Use of prescribed drugs that have a drying effect in the mouth or polypharmacy (e.g. anticholinergics, antihistamines, opioids, antipsychotics antidepressants, diuretics)		✓	
▶ <b>Diabetes</b>		✓	
▶ <b>Immunosuppression</b>			
○ HIV or AIDS		✓	
○ Congenital immunosuppression			✓
○ Immunosuppressant treatment (including chemotherapy)		✓	
○ Hematopoietic cell transplant			✓
○ Use of corticosteroids (inhalation, topical or systemic)		✓	
▶ <b>Dental prostheses</b>			
○ Continuous wear	✓		
○ Poorly adjusted	✓		
○ Poor hygiene of prostheses	✓		
▶ <b>Poor oral hygiene and care practices</b>	✓		
▶ <b>Use of tobacco</b>	✓		

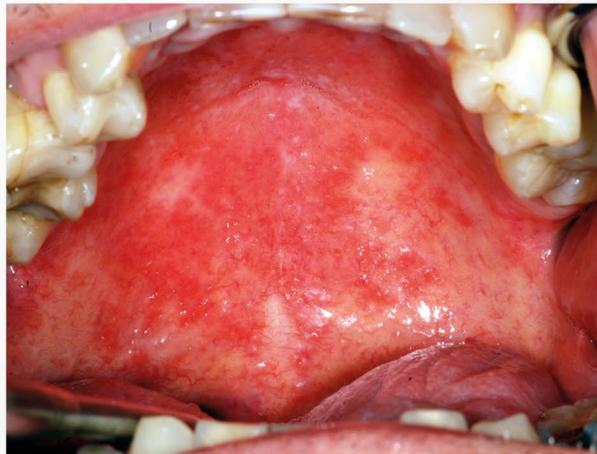
*In the absence of any of the risk factors listed above, consider the presence of non-diagnosed immunosuppression such as a HIV infection.*

CLINICAL PRESENTATION OF ORAL CANDIDIASIS

**Acute pseudomembranous candidiasis (thrush)**



**Erythematous candidiasis**



## ORAL CANDIDIASIS (CONT'D)

### Median rhomboid glossitis



### Prosthetic stomatitis



### Angular cheilitis (perleche)



## ORAL CANDIDIASIS (CONT'D)

### Secondary oral candidiasis associated with inhaled corticosteroid use



OTHER CLINICAL CONDITIONS

Lichen planus

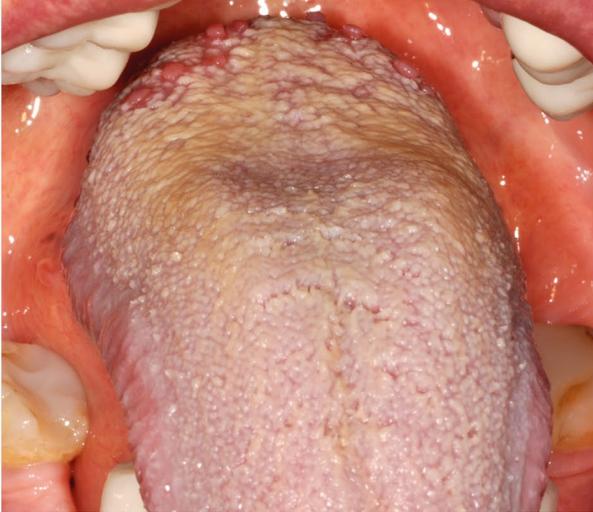


Geographic tongue



## OTHER CLINICAL CONDITIONS (CONT'D)

### Furry tongue and black hairy tongue



### Leukoplakia (white lesions with a malignant transformation potential)



### Aphthous ulcer



## OTHER CLINICAL CONDITIONS (CONT'D)

**Frictional keratosis due to the use of poorly adapted prostheses**

